REMARKS

Amendments to the Claims

Claims 1-7 are pending in the application. Claim 1 has been amended. Support for this amendment can be found, for example, in ¶ [0233] of the published application. This amendment does not constitute new matter.

Rejection of Claims under 35 U.S.C. § 103(a)

Claims 1, 2 and 4-6 are rejected under 35 U.S.C. §103(a) as being unpatentable in light of U.S. Pat. No. 5,437,982 to Catterall et al. ("Catterall") in view of Connolly et al., Biosensors and Bioelectronics, 1990 5: 223-234 ("Connolly"). Claims 1-6 are also rejected under § 103(a) as unpatentable over Catterall and Connolly in view of Tung et al., Biophysical Journal, 1992, 63(2): 371-386 ("Tung"). Finally, Claims 1, 2 and 4-7 are rejected under § 103(a) as unpatentable over Catterall and Connolly in view of WO 96/41166 to Tsien et al. ("Tsien") or Denyer et al., Drug Discovery Today, 1998, 3(7): 323-332 ("Denyer"). To establish a *prima facie* case of obviousness there must be a teaching or suggestion of all the claim limitations. M.P.E.P. § 2142.

Independent Claim 1 is not obvious in view of Catterall and Connolly. Independent amended Claim 1 recites a "method of screening a plurality of drug candidate compounds against a target ion channel comprising . . . modulating a transmembrane potential of said host cells in said plurality of sample wells with a repetitive application of electric field pulses applied with extracellular electrodes so as to set said transmembrane potential to a level corresponding to a pre-selected voltage dependent state of said target ion channel, wherein a frequency of the electric field pulses (*f*) is within the range $\tau_M^{-1} \leq f \leq \tau_b^{-1}$ where τ_M is a time constant for decay of transmembrane potential changes, and τ_b is an average target ion channel open time."

Catterall discloses a method of assaying compounds by introducing a peptide into a cell and then applying a series of pulses at different voltages. In Catterall the ion channel is cycled between different voltage dependent states so that there is significant binding of the peptide. Catterall, however, does not disclose or suggest the use of extracellular electrodes. Instead, Catterall uses a patch clamp technique to directly control transmembrane potential of a single

cell. Thus, the method of Catterall cannot be used with populations of cells and the method is not valuable for high throughput screening.

However, the Examiner uses Connolly to supply the external electrodes. Most of Connolly teaches monitoring electrically activity of cells. Near the end of the article, however, Connolly states that a 1 Hz square wave can be used to initiate beating in cardiac cells. Connolly does not teach that the "frequency of the electric field pulses (*f*) is within the range $\tau_M^{-1} \leq f \leq \tau_b^{-1}$ where τ_M is a time constant for decay of transmembrane potential changes, and τ_b is an average channel open time." Connolly merely points out that myocytes will start beating when exposed to an electric field pulse. However, there is no indication in Connolly (or Catterall) that extracellular electrodes could be used to control transmembrane potential in a manner that allows drug candidate testing protocols to be effectively performed. Prior to the present invention, it was not expected that pulse application protocols with external electrodes could accomplish this. Claim 1 now recites with additional specificity the types of pulse protocols that are often optimal for these types of procedures. These external electrode pulse protocols are not taught or suggested in the prior art.

Neither Catterall nor Connolly teach or suggest "modulating a transmembrane potential of said host cells in said plurality of sample wells with a repetitive application of electric field pulses applied with extracellular electrodes so as to set said transmembrane potential to a level corresponding to a pre-selected voltage dependent state of said target ion channel, wherein a frequency of the electric field pulses (*f*) is within the range $\tau_M^{-1} \leq f \leq \tau_b^{-1}$ where τ_M is a time constant for decay of transmembrane potential changes, and τ_b is an average target ion channel open time." Because neither reference teaches or suggests this element of amended Claim 1, all of the elements of amended Claim 1 are not taught by the combination of Catterall and Connolly. Thus, the combination of Catterall and Connolly does not render amended Claim 1 obvious. Applicants respectfully request the Examiner's rejection of amended independent Claim 1 and the claims that depend therefrom be reconsidered and withdrawn.

Additionally, the combination of Catterall, Connolly and Tung do not render Claims 1-6 unpatentable. The Examiner notes that the combination of Catterall and Connolly "do not expressly disclose repetitive application of biphasic electric fields" and cites Tung as teaching "strength-duration curves derived from field stimulation show that over a wide range of pulse

durations, biphasic waveforms can recruit and activate membrane patches about as effectively as can monophasic waveforms having the same total pulse duration." As noted above, however, the combination of Catterall and Connolly does not teach or suggest all of the elements of amended independent Claim 1. Tung does not cure this deficiency. Thus, the combination of Catterall, Connolly and Tung do not render obvious amended Claim 1 and the claims dependent therefrom.

Finally, the combination of Catterall and Connolly with Tsien or Denyer does not render unpatentable Claims 1, 2 or 4-7. As noted above, the combination of Catterall and Connolly fails to teach or suggest all of the elements of amended independent Claim 1. Neither Tsien nor Denyer remedies that deficiency. Indeed, the Examiner cites Tsien and Denyer only to teach the use of voltage sensors or radiotracers respectively. Thus, Applicants respectfully request that the Examiner's rejection of independent amended Claim 1 be reconsidered and withdrawn. Claims 2-7 are dependent on amended Claim 1, and it is respectfully submitted that these claims are also patentable for at least the same reasons as set forth above with regard to amended Claim 1.

Provisional Rejection of Claims for Double Patenting

Claims 1-7 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application Serial No. 11/444,214. It is respectfully submitted that the above amendment also obviates the double patenting rejection over the claims of 11/444,214.

CONCLUSION

The Applicants have endeavored to address all of the Examiner's concerns as expressed in the previous Office Action. Accordingly, arguments in support of the patentability of the pending claim set are presented above. In light of these amendments and remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested.

If any issues remain that could be resolved by telephone, the Examiner is invited to call the undersigned directly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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